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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/463,480	SINGH ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2002 and 01 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-21* is/are pending in the application.

4a) Of the above claim(s) *6-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,5 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *29 November 2002* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☒ Interview Summary (PTO-413) Paper No(s). 21 .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

1. The cancellation of claims 1-3, the amendment of claims 4-5 and the addition of claim 21 requested in Paper No. 18, filed 1 March 2002 have been entered. The amendments to the specification filed 29 November 2002 have been entered. Claims 4-21 are pending.

2. The restriction mailed 10 May 2001, is modified as below:

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions that are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in response to this action, to elect a single invention to which the claims must be restricted.

Group I, claims 4-5 and 21, drawn to a nucleic acid encoding LGC1.

Group II, claims 4-5 and 21, drawn to a nucleic acid encoding gcH2A.

Group III, claims 4-5 and 21, drawn to a nucleic acid encoding gcH3.

Group IV, claims 4-15 and 19-21, drawn to a LGC1 promoter and a method of using it to induce male sterility.

Group V, claims 4-7, 11-14 and 19-21, drawn to a gcH2A promoter and a method of using it to induce male sterility.

Group VI, claims 4-7, 11-14 and 19-21, drawn to a gcH3 promoter and a method of using it to induce male sterility.

Group VII, claims 16-18, drawn to a construct comprising a LGC1 promoter and a transposase coding sequence.

Claims 1-7, 11-14 and 19-20 will be examined to the extent they read on the elected invention.

The inventions listed as Groups I-VII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The nucleic acids of each invention are unrelated, each to each other. Further, where, for example, claims 1-5 do not require a nucleic acid of specific sequence, it is apparent that Tuttle et al (1995, US Patent 5,477,002) discloses anther-specific cDNAs where at least one would be specifically expressed in generative or sperm cells or a derivative of such a gene wherein said DNA renders claim 1, among the others, not novel. Thus, the technical feature of the polynucleotide sequence is not special and the groups are not linked under PCT Rule 13.1 to form a single general inventive concept.

Inventions I-III are unrelated to inventions IV-VII. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different modes of operation, different functions, and different effects. The promoters of inventions IV-VII can be used to direct the expression of genes other than those of inventions I-III, for example, a ribonuclease. Alternatively, the genes of inventions I-III can be expressed under promoters other than those of inventions IV-VII, for example, the CaMV 35S promoter or a light-inducible promoter.

Inventions I-III are unrelated to each other, as are inventions IV-VI unrelated to each other. Applicant is reminded that nucleotide sequences encoding different proteins are structurally distinct chemical compounds and are unrelated to one another, as are different promoters structurally distinct chemical compounds. These sequences are thus deemed to normally constitute **independent and distinct** inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleotide sequence is presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141 et seq. This requirement is not to be construed as a requirement for an election of species, since each nucleotide and amino acid sequence is not a member of single genus of invention, but constitutes an independent and patentably distinct invention.

Group IV is unlinked to Group VII. Both groups are drawn to DNA constructs comprising promoters of sperm-specific promoters, including but not limited to those with 50% identity to the LGC1 promoter. As these constructs are not drawn to a single promoter sequence, but a multitude of sperm-specific promoters, unity of invention is lacking. Additionally, Group VII requires a transposase coding sequence, not required by Group IV, and Group IV requires a cytotoxic nucleic acid, not required by Group VII.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter and fields of search, restriction for examination purposes as indicated is proper. Additionally, a search of more than one sequence would represent an undue burden on PTO resources.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

During a telephone conversation with Frank Digiglio on 21 February 2003 a provisional election was made with traverse to prosecute the invention of Group I, claims 4-5 and 21 to the extent they read on a nucleic acid encoding LGC1 (nucleic acids of SEQ ID NO:3 or that encode SEQ ID NO:4). Affirmation of this election must be made by applicant in replying to this Office action. Claims 6-20 and sequences SEQ ID NO:5-8 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. The abstract is not descriptive of the instant invention, which is a nucleic acid that is specifically expressed in generative cells and sperm cells but doe not encode a histone. A new abstract is required that is clearly indicative of the invention to which the claims are directed. The abstract of the disclosure should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

Claim Rejections - 35 USC § 101

5. Claims 4-5 and 21 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well-established utility. The rejection is repeated for the reasons of record as set forth in the Office action mailed 17 August 2001, as applied to claims 1-5. Applicant's arguments filed 1 March 2002 have been fully considered but they are not persuasive.

Applicant urges that the claimed genes are specifically expressed in male gametes, and the specification on pg 3, lines 4-7, asserts that the genes and promoters enable specific genetic manipulation to generate male sterile plants and male gamete specific transposon tagging. Applicant further urges that the claimed male gamete-specific nucleic acids are useful in production of hybrid plants, and thus the utility requirement is met (response pg 3-4).

This is not found persuasive because without knowledge of the function of LGS1, generation of male sterile plants is not a specific utility.

While the specification suggests making male sterile plants by fusing a toxin gene to a gene naturally operably linked to the LGC1 male-gamete specific promoter (pg 12, lines 5-7), such a method of making male sterile plants requires the LGC1 promoter, which is not part of SEQ ID NO:3. Additionally, as any protein-encoding region can be used in a toxin fusion construct under control of a male-gamete specific promoter, such a use is not specific to SEQ ID NO:3.

Similarly, male gamete specific transposon tagging via a gene of unknown function is not a specific utility, as utility requires knowledge of the function of the protein encoded by SEQ ID NO:3.

As no description of the function of the LGS1 is provided, the protein can have no well-established utility. Thus, the invention has no specific asserted or well established utility.

It is unknown how and under what conditions a nucleic acid like SEQ ID NO:3, encoding an protein of unknown function, could be used to make male-sterile plants. Does one skilled in the art want to increase the activity of the encoded protein, and in what organ, tissues or cell types? It is apparent that extensive further research, not considered to be routine experimentation, would be required before one skilled in the art would know how to use the claimed invention. It has been established in the courts that a utility that requires or constitutes carrying out further research to identify or reasonably confirm a "real world" context of use is not a substantial utility:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point-where specific benefit exists in currently available form, there is insufficient justification for permitting an application to engross what may prove to be a broad field (*Brenner v. Manson*, 383 U.S. 519 (1966)).

Thus, while making male sterile plants would provide substantial benefit to the public, it is unclear how one of ordinary skill in the art would be able to utilize SEQ ID NO:3 to control any physiological processes without having to carry out further research. Accordingly, the claimed invention lacks a "real-world" use.

Claim Rejections - 35 USC § 112

6. Claims 4-5 and 21 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. The rejection is repeated for the reasons of record as set forth in the Office action mailed 17 August 2001, as applied to claims 1-5. Applicant's arguments filed 1 March 2002 have been fully considered but they are not persuasive.

Applicant arguments are summarized above. They are not found persuasive for the reasons above.

7. Claims 4-5 and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicant's arguments filed 1 March 2002 to a scope of enablement rejection have been fully considered but they are not persuasive.

The claims are broadly drawn to nucleic acids that encode a protein with 90% identity to SEQ ID NO:4 or derivatives of such a nucleic acid.

The instant specification only provides guidance for isolation of LGC1 (SEQ ID NO:3) by differential hybridization of a lily cDNA library (example 1); Northern hybridization using RNAs from various lily tissues to show that LGC1 is not expressed in leaf and stem cells but is expressed in pollen generative cells and conformation of that using *in situ* hybridization (example 1). Example 2 teaches isolation of two lily male-gamete expression-specific histone

genes, SEQ ID NOs:6 and 8. Examples 3-5 teach the cloning the LGC1 promoter (SEQ ID NO:9) using Uneven PCR, constructs using that promoter and LGC1 promoter/GUS fusions to demonstrate its expression pattern.

The instant specification, however, fails to provide guidance for the isolation or construction of nucleic acids that encode a protein with 90% identity to SEQ ID NO:4, for derivatives of such a nucleic acid, or for use of SEQ ID NO:3. For example, the instant specification fails to provide guidance for exact hybridization or amplification conditions and probes/primers to use in isolation of nucleic acids other than SEQ ID NO:3.

Making derivatives of a protein-encoding region is unpredictable. Even making "conservative" substitutions (*e.g.*, substituting one polar amino acid for another, or one acidic one for another) does not produce predictable results. Lazar et al (1988, Mol. Cell. Biol. 8:1247-1252) showed that the "conservative" substitution of glutamic acid for aspartic acid at position 47 reduced biological function of transforming growth factor alpha while "nonconservative" substitutions with alanine or asparagine had no effect (abstract). Similarly, Hill et al (1998, Biochem. Biophys. Res. Comm. 244:573-577) teach when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the "nonconservative" amino acid glutamine, there is little effect on enzyme activity, while the substitution of one of those histidines with the "conservative" amino acid arginine drastically reduced enzyme activity (see Table 1).

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate

nucleic acids encoding proteins with 90% identity to SEQ ID NO:4. Making all possible single amino acid substitutions in an 128 amino acid long protein like that encoded by SEQ ID NO:3 would require making and analyzing 19^{128} nucleic acids; these proteins would have 99.2% identity to SEQ ID NO:4. Because nucleic acids encoding proteins with 90% identity to SEQ ID NO:4 would encode proteins with 12 amino acid substitutions, many more than 19^{128} nucleic acids would need to be made and analyzed.

As the specification does not describe the function of the protein of SEQ ID NO:4 and does not teach how to assay for it, undue trial and error experimentation would be required to screen through the myriad of nucleic acids encompassed by the claims, to identify those that encode a protein with the same function as SEQ ID NO:4, if such nucleic acids are even obtainable.

The specification does not teach how to use a nucleic acid of SEQ ID NO:3. As the function of the encoded protein is not disclosed, one of skill in the art would not know how to use it. As discussed above, it is apparent that extensive further research, not considered to be routine experimentation, would be required before one skilled in the art would know how to use the claimed invention.

Given the claim breath, unpredictability in the art, undue experimentation, and lack of guidance in the specification as discussed above, the instant invention is not enabled.

Applicant urges that the claims as amended are drawn to an isolated nucleic acid that is specifically expressed in generative cells and sperm cells and encodes a protein with 90% identity to SEQ ID NOs:4, 6 or 8. Applicant also urges that the specification teaches isolation of

SEQ ID NOs:3, 5 and 7, and how to determine the male gamete specific expression of these sequences (response pg 4-6).

This is not found persuasive. Male-gamete specific expression of SEQ ID NO:3 is a function of its promoter, not a function of SEQ ID NO:3 or its protein, SEQ ID NO:4. The specification does not teach the function of SEQ ID NO:4, and thus no assay for nucleic acids that encode proteins with 90% identity or that are derivatives of SEQ ID NO:3 is provided.

8. Claims 4-5 and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is modified from the rejection set forth in the Office action mailed 17 August 2001, as applied to claims 1-5. Applicant's arguments filed 1 March 2002 have been fully considered but they are not persuasive.

The claims are broadly drawn to a multitude of DNA molecules that encode a protein with 90% identity to SEQ ID NO:4 or that are derivatives of such a gene. In contrast, the specification only describes a coding sequence from lily that comprises SEQ ID NO:3. The specification fails to provide a description of the function of the encoded LSC1 protein. Applicant does not describe other DNA molecules encompassed by the claims, and the structural features that distinguish all such nucleic acids from other nucleic acids are not provided.

Hence, Applicant has not, in fact, described DNA molecules that encode a protein with 90% identity to SEQ ID NO:4 or that are derivatives of such a gene within the full scope of the

claims, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and physical characteristics of the claimed compositions, it is not clear that Applicant was in possession of the genus claimed at the time this application was filed.

Applicant urges that the claims as amended are drawn to an isolated nucleic acid that is specifically expressed in generative cells and sperm cells and encodes a protein with 90% identity to SEQ ID NOs:4, 6 or 8. Applicant also urges that the law does not require a reduction to practice to satisfy the written description requirement. Applicant urges that the claimed nucleic acids are described with sufficiently detailed, relevant identifying characteristics, *i.e.*, their male gamete-specific expression and their encoding a protein with 90% identity to one of SEQ ID NOs:4, 6 or 8 (response pg 6-7).

This is not found persuasive because male-gamete specific expression of SEQ ID NO:3 is a function of its promoter, not a function of SEQ ID NO:3 or its protein, SEQ ID NO:4. Thus, nucleic acid that encode proteins with 90% identity to SEQ ID NO:4 or that are derivatives of SEQ ID NO:3 are not described.

9. Claims 4-5 and 21are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Dependent claims are included in all rejections. The rejection modified from the rejection set forth in the Office action mailed 17 August 2001, as applied to claims 1-5.

Applicant's arguments filed 1 March 2002 have been fully considered but they are not persuasive.

Claim 4 is indefinite for its recitation of "derivative of said gene" in line 2. The extent to which the derivative differs from the gene, and the nature of those differences, is unclear.

Claim 5 is indefinite for its recitation of "low stringency conditions". What conditions are considered low stringency is unclear. What are the salt concentrations and times for the hybridization and washing steps?

Claim 21 is indefinite in its recitation of "lily or a related plant". What plants are considered related to lily is unclear, as all plants are related to lily to some extent. Applicant urges that the meaning of this phrase would be clear to one of skill in the art (response pg 8). This is not found persuasive because "related" is a relative term. The extent of relationship must be made clear for the metes and bounds of the claim to be clear.

Claim Rejections - 35 USC § 102

10. Claims 4-5 and 21 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Baszczynski et al (1997, US Patent 5,633,438). The rejection is repeated for the reasons of record as set forth in the Office action mailed 17 August 2001, as applied to claims 1-3. Applicant's arguments filed 1 March 2002 have been fully considered but they are not persuasive.

Baszczynski et al teach a nucleic acid, BNM1, whose expression is specific to trinucleate and binucleate microspores (column 19, lines 27-51 and Fig. 2). Thus this nucleic acid is

specifically expressed in generative cells and sperm cells. The nucleic acid was isolated from *Brassica napus*, which is "related" to lily. The nucleic acid would be a derivative of a nucleic acid encoding SEQ ID NO:4 or a protein with 90% identity to SEQ ID NO:4.

Applicant urges that claims 4-5 were previously found free of the art (response pg 8-9).

This is not found persuasive because the instant claims 4-5 and 21 are drawn to an isolated nucleic acid comprising a derivative of a gene specifically expressed in generative cells and sperm cells. Baszczynski et al teach such a nucleic acid.

11. Claims 4-5 and 21 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Tuttle et al (1995, US Patent 5,477,002). The rejection is repeated for the reasons of record as set forth in the Office action mailed 17 August 2001, as applied to claims 1-3. Applicant's arguments filed 1 March 2002 have been fully considered but they are not persuasive.

Tuttle et al teach anther-specific cDNAs expressed at different stages of anther development (Table 1). The nucleic acids were isolated from tobacco, which is "related" to lily. The nucleic acids would be derivatives of a nucleic acid encoding SEQ ID NO:4 or a protein with 90% identity to SEQ ID NO:4.

Applicant urges that claims 4-5 were previous found free of the art (response pg 8-9).

This is not found persuasive because the instant claims 4-5 and 21 are drawn to an isolated nucleic acid comprising a derivative of a gene specifically expressed in generative cells and sperm cells. Tuttle et al teach such a nucleic acid.

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (703) 308-5059. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Customer Service at (703) 308-0198.

Anne R. Kubelik, Ph.D.
February 21, 2003